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THE NUTRITIONAL NEEDS OF THE PREMATURE INFANT

J. A. JOHNSTON, M.D.

Pediatrician-in-Chief

The physiological considerations modifying the food mixture for the premature are: the increased speed of growth, the impairment of renal function, diminished intestinal absorption, incomplete development of enzyme systems, and the deficient antenatal storage of minerals and vitamins.

GROWTH SPEED

It has usually been assumed that in this accelerative phase of the first sigmoid curve of growth, the caloric requirement was higher than that of the baby born at term and entering into the decelerative phase. Levine and Gordon[1] felt that this was not true and that the figure of 120 calories per kilogram was adequate for this age. Using the same mixture, however, (half skimmed milk with about 8 per cent added carbohydrate) that they subsequently studied, we found that consistent gain was achieved on about 130 calories per kilogram.

RENAL FUNCTION

In our concern with the relative amounts of protein, fat, and carbohydrate, little attention has been given until recently to the load imposed on a possibly immaturely functioning kidney by the high mineral content of many of the artificial food mixtures offered. In an interesting study of the comparative loads involved in feeding a conventional evaporated milk, water, and dextrimaltose mixture and an evaporated milk-water mixture without added carbohydrate, Pratt[2] brings out the marked drain on the reserves of body water with the latter. While the kidney seems able to manage this solute load of mineral and urea, it would seem to do so by taxing available water to the utmost, and the occurrence of any added drain, such as imposed by diarrhoea, might well prove fatal.

I was first concerned about this many years ago when, following about a month of apparent progress, we lost a number of prematures with diarrhoeal disease, that in a mature infant I feel sure we could have managed. Other recent studies suggesting a possible relationship between edema and the development of retrolental fibroplasia still await confirmation in the human. But if, as some people feel, retrolental fibroplasia may ultimately be shown to have a viral origin, the development and course of any infection is unfavorably influenced by the oedema state.

INTESTINAL ABSORPTION

Diminished absorption of fat would seem to be the chief reason for the relative increase in calories to be derived from protein and carbohydrates, rather than any

specifically higher need for protein conditioned by the rapid growth. This acc e erated growth is largely cared for by the increased nitrogen retention of the premature. There is a very real question of how much retention should be sought. In any critical evaluation of food mixtures, the criteria of optimal must include many things that we are unable to measure in the human. In work with rats, it can be shown that while rates of gain and the attainment of maturity increased pari passu with increases in nitrogen intake, on the other hand, length of life, reproduction, survival of offspring and possibly resistance to infection were optimal with moderate intakes. In studies of the infant in the first two months of life we have felt that we frequently exceeded tolerance with mixtures in which the protein exceeded 20 per cent of the total calories. This has not seemed to be true with the mixture here described in which part of the nitrogen is given as amino acids. Provision for the oil-soluble vitamins A and D in an absorbable form is made necessary by the defect in absorption of fat.

INCOMPLETE DEVELOPMENT OF ENZYME SYSTEMS

One of the striking findings of Levine and Gordon[3] was the demonstration of an incomplete oxidation of tyrosine and phenylalanine, a defect which was correctable by the giving of large amounts of ascorbic acid—100 mg. daily. This must be included for optimal results.

DEFICIENT STORAGE OF MINERALS AND VITAMINS

To this have been attributed the relatively higher occurrence of rickets and tetany in premature infants. While it is true that the amounts of calcium and phosphorus in breast milk are very low compared to cow's milk, their more favorable ratio and economy of utilization in the presence of adequate amounts of vitamin D make me question their inadequacy even in this period of rapid growth. With these considerations in mind, we have used for about ten years a mixture of whole milk, water, amino acids, and dextrimaltose with which we hoped to achieve reasonable concentration, relatively high but more easily utilized protein, low fat and some reduction in mineral. This mixture is shown in Table I.

Table I—THE HENRY FORD HOSPITAL MIXTURE FOR PREMATURE INFANTS

PASTEURIZED MILK	500 cc.
WATER	500 cc.
PROTOLYSATE	60 gm.
DEXTRIMALTOSE	30 gm.

The chemical analysis of this mixture is shown in Table II.

Table II—THE CHEMICAL ANALYSIS OF THE HENRY FORD HOSPITAL MIXTURE FOR PREMATURE INFANTS

Values in Grams

		P	F	CHO	MIN	Mg	S	K	Na	Cl	Ca	P
Whole Milk	500 ml	17.0	19.0	23.0	3.500	.060	.165	.775	.250	.525	.590	.465
Water	500 ml											
Dextri-Maltose No. 2	60 grams			59.4								
Protolysate	30 grams	22.5			1.650	.015	.180	.090	.450	.450	.120	.360
Total		39.5	19.0	82.4	5.150	.075	.345	.865	.700	.975	.710	.825
Values per	100 ml	3.95	1.90	8.24	.515	.0075	.0345	.0865	.070	.0975	.071	.0825
Values per liter in milliequivalents						6.2	21	22	30	27	36	82.5

20 cals/oz

Nitrogen—.631 gms per 100 ml. of mixture.

	Calories	Calories
Protein	158.0	24%
Fat	171.0	26%
Carbohydrate	330.0	50%
	659.	

The results from this formula are compared with breast milk, and 2 per cent milk with 8 per cent added carbohydrate, in respect to daily gain and hospital days in Table III.

Table III—COMPARATIVE WEIGHT GAINS OF THREE GROUPS OF TEN PREMATURE INFANTS ON VARIED FEEDINGS

Groups	Birth Weight Average and Range	Feeding	Gain per Day	Hospital Days
I	1692 gms. 1265-1960 gms.	Breast Milk	24.6 gms.	34.2
II	1709 gms. 1240-2800 gms.	2% Skimmed mild with 8% added carbohydrate	21.5 gms.	32.
III	1546 gms. 1060-1850 gms.	Ford Hospital Mixture*	22.6 gms.	36.4

*Whole milk 500 cubic centimeters, water 500 cubic centimeters, protolysate 60 grams, dextrimaltose 30 grams.

On this mixture clinical results have been good. Comparative gains in weight are admittedly an inadequate criterion, but I have not seen the nutritional breaks with diarrhoea that we formerly saw.

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CONGENITAL TUBERCULOSIS

GEORGE B. KEMPTON, M.D.*
PHILIP J. HOWARD, M.D.**

The diagnosis of congenital tuberculosis is rare in this country. Probably the first case was reported by Schmorl and Birch-Herschfeld in 1890 (1). In 1935, Beitzke (2) analysed one hundred cases from the literature and showed that only sixty-one of these were proven. He set up definite criteria which will be quoted: 1. The nature of the lesion must be proved. 2. A primary complex in the foetal liver is proof of congenital tuberculosis since it can only have arisen from tubercle bacilli in the blood of the umbilical vein. 3. If there is no primary infection of the liver, a diagnosis can be made only, first, if there are tuberculous changes in the foetus in utero, at birth, or within a few days of birth, or, second, in a child who lives longer than a few days, if extra-uterine infection can be excluded with certainty, the child being immediately separated from the mother, and kept in an environment free from tubercle bacilli. Jordan and Spencer (3) in 1949, distinguished two main types,—infection reaching the foetus by way of the umbilical vein, and infection arising from infected amniotic fluid with ingestion of the bacilli. Loewenstein (4), in 1935 cultured the blood of fifty-nine parturient women with pulmonary tuberculosis, together with the blood from the umbilical vein, and found positive cultures for tubercle bacilli in both bloods in eleven cases. The suggestion is apparent in this work that some congenital tuberculosis is not fatal if the infection is mild. If the child survives the first twelve months, resistance to the tubercles may become sufficient to allow healing and complete recovery. Siegel and Singer (5), however, in 1935, attempted to demonstrate tubercle bacilli in infants of mothers with far advanced pulmonary tuberculosis. Careful cultures were made of the infants blood at birth in the fifteen cases studied. There was only one positive culture, and in this case, the placenta itself was tuberculous. They concluded that tubercle bacilli seldom passed the placental barrier. Hughesdon (6) in 1946 reported four new cases, and reviewed 115 proved cases. It is interesting to note a large series presented by Elizalde and Latienda (7) in 1945. Sixteen cases were reported in which the infants were immediately separated from their mothers, and cared for under strict conditions. Additional cases (3,8,9, 10,11,12,13,14) have appeared bringing the total at least to 144. This subject has been brought to our attention by the following child.

Infant Dennis B., Case Number 560714, age 14 hours, was admitted to the hospital for boarding care. He was born at the Pontiac State Hospital where his mother was a mental patient also having tuberculous peritonitis. He weighed six pounds at birth, and left the Pontiac Hospital at 12 hours of age, having had no contact with the mother after delivery. Physical examination on admission showed a normal white male infant with temperature of 98° F. The course in the

*Formerly resident in the Department of Pediatrics. Now practicing in Jackson, Michigan.
**Associate in the Department of Pediatrics.

hospital was uneventful with adequate weight gain until the fifteenth day, when the baby had a temperature of 101.8° F. Examination revealed occasional moist rales in both lung fields, and moderate serous nasal discharge. Penicillin and sulfadiazine were started but the fever did not decline. A chest x-ray revealed a generalized pneumonia, with some ateleclasis. After two days of streptomycin, the temperature reached normal on the twentieth hospital day. He continued to take formula well, but his weight gain was interrupted. His temperature was normal until the thirty-second day. X-ray of the chest now showed a generalized nodular type of infiltration scattered throughout both lung fields. Tubercle bacilli were isolated from the gastric washings. Guinea pigs inoculated with the gastric washings showed tuberculosis of the spleen and lymphatic glands. The patient followed a progressive down-hill course, despite continued streptomycin and supportive therapy, and expired on the one hundred and fifth hospital day.

Post mortem study showed on the visceral pleura of the lungs, numerous firm, yellow, purplish nodules. These nodules were present everywhere in the parenchyma causing great increase in density throughout. The nodules measured 1.0 cm. in diameter and often contained yellow soft material. The bronchi contained purulent yellow fluid which was at times bloodstained. The bronchial nodes appeared to be involved. In the fascia around the hilus of the spleen, tubercles were visible. No gross pathology was apparent in the liver.

Microscopic examination of the lung sections showed marked involvement by tubercles characteristic of this disease. They were numerous and seen throughout the lung fields, including the bronchial nodes. Some tubercles showed signs of healing characteristics of streptomycin therapy. A few small tubercles were seen in the spleen, and also infrequent small tubercles in the liver. No other areas of tuberculosis were found in the body.

This is a case of congenital tuberculosis satisfying the criteria of Bertyke (1). The tuberculous lesion was proven. The infant was separated from his mother immediately and kept in an environment free from tuberculosis. Every nursery attendant was x-rayed. As the lesions were primarily pneumonic, the infection by all odds probably entered by inhaled and ingested infected amniotic fluid, the second type of Jordan and Spencer (2). This discussion and case are presented because the condition is extremely rare in our country.

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SPECIAL TYPES OF ESCHERICHIA COLI IN INFANT DIARRHEA

Wm. W. Ferguson, Ph.D.*

Approximately eight years have passed since the work of John Bray[1,2] in England drew the attention of English and Scotch workers to the possible role of a certain *Escherichia coli* type in infant diarrhea. Abroad a voluminous literature has been published on this subject, most of it favorable to the idea that one, and perhaps two, serologic types of *E. coli* are among the causative agents of infant diarrhea.

With what sort of a reception has this work been received abroad and in this country?

One is inclined to believe, because of the number of publications that have come from England and Scotland, that in those countries, at least, acceptance of certain coliform bacteria as etiologic agents in diarrhea of infants has been widespread. Apparently, though, nothing is further from the truth. To use a newspaper cliché, a "reliable source" has informed me that pediatricians, pathologists, and bacteriologists over there are still divided into two camps over the issue of whether or not *Escherichia coli* has anything to do with gastroenteritis of babies. Also, according to the "reliable source" feeling runs rather high among the partisans. Nevertheless, an annotation in the editorial section of the Lancet of August 16, 1952, states unequivocally that one serologic type of *E. coli* may cause infantile gastroenteritis both as a sporadic and epidemic disease.

Probably the situation in Sweden, Denmark, Germany and other continental countries is much the same as in England. However, the medical literature in those countries appears to be favorable, perhaps because the opposition has not been active in publication.

In this country, if one were to judge by publications and editorials in medical journals, there is complete indifference to the subject. So far as I am aware, not a single article has appeared in any of our pediatric or other strictly clinical journals on special serotypes of *Escherichia coli* in infant diarrhea. Publications to date have come from bacteriologists, some of whom are men with a medical degree. I know of one and perhaps two papers on coli diarrhea of infants which is under preparation by a well-known pediatrician. These will be the first clinical papers of the kind to be published in the U. S. A. It seems likely that there will be others when the right combination of medical and laboratory skills is available.

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*Coordinating Bacteriologist, Division of Laboratories, Michigan Department of Health, Lansing, Michigan.

Presented before the Michigan Academy of Pediatrics, Henry Ford Hospital, February 18, 1953.

It is a heartening sign that investigators and reviewers are coming to recognize that diarrhea of the newborn may be caused by a variety of agents, both bacterial and viral. There was a time shortly after the publications of Buddingh and Dodd[3], and of Light and Hodes[4], when reviewers were prone to discuss infant diarrhea solely in terms of a virus etiology.

One of the open minded—Clifford[5] of the Harvard Medical School—feels that the syndrome described as epidemic diarrhea of the newborn is not a pathologic entity but a miscellaneous group of cases of various etiologies, known and unknown, bound together by a common symptom—diarrhea.

Kirby, Hall and Coackley[6] of England share this view and feel that on the basis of the literature the syndrome of infant diarrhea may be broken down into six categories, according to clinical symptoms and etiologic agents.

Apparently, though, it has taken this concept some time to take root in the minds of medical investigators. Even today there is an inclination on the part of some to regard infant diarrhea as an entity with a virus as the sole causative agent.

John Bray, in England, back in 1943, evidently had an open mind about the etiology of infant gastroenteritis. His unorthodox approach to the problem is a tribute both to himself and his colleague Beavan. It was Beavan, a clinician, who suggested to him that he determine the cause of the unusual seminal odor which had been noted in the stools of diarrheal babies in outbreaks of the disease. His investigation of this lead resulted in the discovery of a single serologic type of *E. coli* organism which produced a seminal odor on artificial media and, moreover, which was present in the stools of a large percentage of diarrheal babies. The organism was found in only a small number of well babies housed in the diarrheal wards in which he conducted his studies. The name Bray gave his coliform organism was *Bact. coli* var. neapolitanum—a name now of historical interest only, since it has been supplanted by a variety of designations.

At about the time Bray concluded his work, Giles, Sangster and Smith[7], working in Aberdeen, Scotland, began studies on infant diarrhea, keeping in mind the possibilities of a bacterial or viral agent. Their search for a virus was soon dismissed as useless; likewise their search for Group D streptococci was discontinued as futile. In their search for special types of *E. coli*, however, they hit "pay dirt."

During 1947, Giles, Sangster and Smith[7] investigated 207 cases of infective gastroenteritis, chiefly in infants who were bottle-fed and under 7 months of age. Of these, 105 or 50.6 percent died. From the stools of 95 percent of the infants a special coliform organism was isolated which they named *Bact. coli* alpha. It was later discovered that *Bact. coli* alpha was identical with the coli organism of Bray.

At post-mortem 55 of the fatal cases in the Aberdeen study showed an indefinite pathology, apparently a common finding in infant diarrhea. The changes that occurred in the intestines were termed minimal, but the liver was affected in some instances, showing slight to extensive fatty degeneration.

Sera of 21 out of 41 infants who excreted the alpha organism were found to have an antibody titer varying from 1 in 40 to 1 in 640, while no significant agglutinins for *B. coli* alpha were detected in the sera of 53 normal infants. A study of fecal material from normal children and normal adults revealed that *Bact. coli* alpha was present in a very small percentage of cases.

During the latter part of 1948, the Aberdeen group found that the alpha organism occurred infrequently in diarrheal infants in that area. Instead a new type of coliform bacterium, called *Bact. coli* beta, appeared with increasing frequency. During 1949-50[8] the beta type occurred in infant diarrhea nearly to the exclusion of the alpha type. At the same time a considerable lowering of the mortality rate took place. It seems possible that better care, together with the use of chloromycetin, influenced the death rate, perhaps as much as a change in the type of organism.

The next work of significance was reported in 1949 by the English workers Taylor, Powell and Wright[9] who investigated outbreaks of diarrhea and vomiting among infants in several nurseries located in the London area. They found no recognized pathogenic bacteria but demonstrated a single serologic type of *Escherichia coli* organism in a high percentage (100 and 91) of infants in 2 nurseries; a moderate percentage (43) in a third nursery; one fifth of the cases in a fourth nursery; and none in a residential nursery with endemic diarrhea and vomiting. Their coliform organism they called *Bact. coli* D_{433}, but it was identical serologically and biochemically with the organism of Bray, and with *Bact. coli* alpha.

Bact. coli D_{433} was not isolated from 208 normal babies, nor was it found 3 to 6 months later in 82 infants occupying nurseries and wards where it had been found earlier. The organism was found, however, in 4 of 84 adult contacts and from 9 of 34 baby contacts.

Attempts to demonstrate a virus in post-mortem material from 4 babies who had excreted *Bact. coli* D_{433} were unsuccessful. A variety of animals was used and various routes of inoculation were attempted. This work, carried out by F. O. MacCallum[9], is the only significant attempt to date to demonstrate a virus in either post-mortem or fecal material from infants infected by one of the special coliform organisms.

* * * *

The work just reviewed should justly be considered the pioneer work which other investigators have expanded or have challenged. It is not possible at present, nor would your patience tolerate, a detailed review of all the publications which have been made on this subject. Instead, I wish to sum up for you the evidence for and against regarding these bacteria as causative agents of diarrhea in infants.

First, though, in the interests of sanity, it is necessary to clear up the matter of nomenclature of the special *E. coli* organisms. The British Medical Journal urges that the designations of Kauffmann, the Danish bacteriologist, be accepted internationally. For that reason I shall use the Kauffmann formula 111, B_4 for

the organism first described by Bray, and formula 55, B_5 for the *B. coli* beta of Giles, Sangster and Smith.

The following points are presented on the "pro" side of the argument in regard to etiology:

Point 1. From the standpoint of geographic distribution it is clear that *E. coli* 111, B_4 is not a purely local type, but has been found associated with infant diarrhea in England[1,9], Scotland[7,8], Sweden[10], Germany[11], Denmark[12], France[13], the U. S. A.[14,15], The Netherlands[16], Israel[17], Mexico[18], and Japan[19]. This type is either more virulent than *E. coli* 55, B_5 or else more widely distributed; or perhaps its virulence accounts for its more frequent discovery and therefore its apparent wider distribution. The 55, B_5 type has been found in Scotland, in England, in Michigan, and within the last year in Montreal, Canada[20].

Point 2. It is noteworthy that in infant diarrhea the special coliform organisms, when present, are found in nearly pure culture in the feces during the diarrheal stage. In convalescent infants who have received no treatment, both the 111, B_4 or 55, B_5 organisms tend to disappear and are replaced by other flora.

Point 3. Of particular interest is the fact that *E. coli* 111, B_4 has been found frequently in the nasopharynx of diarrheal infants excreting the same organism in the feces. Neter, Webb et al.[21] have pointed to the analogy to Salmonella infection in infants in which the same observation has been made.

Point 4. Chloromycetin, aureomycin, terramycin, and lately, neomycin have been found effective in the treatment of diarrheal infants infected with the 111, B_4 organism. It has been noted by some investigators that as clinical improvement occurs after therapy, the special coliform organism disappears from the nasopharynx and stools.

Point 5. It is controversial in England, at least, as to whether or not infected infants develop an agglutinin titer for 111, B_4 organisms. The evidence of Giles, Sangster and Smith[7] has been quoted. We have found in Michigan titers of 1:256 in convalescent infants. Dutch investigators[16] also report the development of agglutinins in infants who have had diarrhea in which this bacterium was present.

Point 6. Our staff at Lansing has carried out fairly large-scale feeding experiments[22,23] on adult volunteers during the last two years, using 111, B_4 and 55, B_5 organisms. These tests convince us that both types of bacteria are markedly different than *E. coli* from normal individuals. A total of 114 men were used in the first experiments and 71 in the second. It was demonstrated that 111, B_4 organisms in large dosage would cause gastroenteritis similar to food-poisoning, and that individuals ingesting the test cultures developed specific agglutinins for them. The 55, B_5 type produced milder but definite symptoms of gastroenteritis. *E. coli* organisms from normal babies produced no illness even when fed in very heavy dosage. In addition, no volunteer showed an agglutinin rise from ingesting the latter type of culture.

The work of Neter and Shumway[14] may be known to many of you, but it will bear repeating. These investigators fed a 2 month-old infant with congenital defects 100 million *E. coli* 111, B_4 organisms, in formula, and produced diarrhea and weight loss within 24 hours. The organism was subsequently demonstrated both in the nose and throat and in feces. Clinical improvement followed treatment with terramycin and the organism disappeared within 48 hours after therapy was begun.

Point 7. Rogers[24], Rogers and Koegler[25] in Birmingham, England, have presented bacteriologic evidence of how epidemics of infantile gastroenteritis spread from hospital to hospital, as well as within hospital wards. They have described three such outbreaks, in 2 of which the *E. coli* 111, B_4 organism was associated with the cases of diarrhea, and another in which the 55, B_5 type was present. The epidemiological evidence is strong, according to them, that both types of *E. coli* are of etiologic significance in certain epidemics of infant diarrhea.

In presenting considerations against regarding the special *E. coli* organisms (particularly the 111, B_4 type) as among the causative agents of infant diarrhea, I admit that I am handicapped by a definite inclination toward the "pro" side of the argument. However, there is another side.

Point 1. about which there can be no disagreement, is the fact that no one, as yet, has carried out careful, large-scale attempts to demonstrate a viral agent in material from diarrheal infants excreting either *E. coli* 111, B_4 or 55, B_5. Until this is done, perhaps with humans as test animals, there will always remain a doubt. It has been pointed out by Bray[1] that the presence of *E. coli* 111, B_4 in infant diarrhea may be analogous to the situation in hog cholera, where a virus is the causative agent but *Salmonella choleraesuis* is frequently present.

Point 2. The majority of investigators have found the 111, B_4 type to occur in only a small number of the normal individuals examined. Two papers, however, have been published which cast some doubt on this point. The work of Payne and Cook[26], and of Cathie and MacFarlane[27], needs careful consideration, for they have found quite a number of strains of 111, B_4 in non-diarrheal infants. It may be that in both normal infants and adults many carriers exist, just as Salmonella carriers exist in all age groups. The authors cited, however, present their findings as reasons for not regarding the 111, B_4 organism as a pathogen.

Point 3. In some outbreaks of infant diarrhea the special coliforms have been found in only a varying percentage of diarrheal babies. Why were they not present in all infants affected?

I cannot answer this, but I will hazard a guess that part of the difficulty may be the inadequacy of selective media for demonstration of the organisms sought. During the diarrheal stage, if an infant has not received treatment with antibiotics, selective media are not important. The organisms are nearly always very abundant. However, if treatment has begun, discharge of the coliforms may be intermittent or the number may be small.

Point 4. One would think that organisms capable of causing severe diarrhea in one type of mammal would cause distinct symptoms when tested in other animals. This is apparently not the case with *E. coli* 111, B_4. Taylor[9] made repeated attempts to demonstrate some difference in pathogenicity between the 111, B_4 type and serologically unrelated coli strains isolated from healthy babies. All strains gave much the same results when given to guinea pigs, mice, rabbits or monkeys, the degree of pathogenicity being dependent upon the route of inoculation.

Point 5. It is very difficult for pediatricians or bacteriologists to accept as a pathogen a member of a bacterial group regarded as essentially commensal in the intestinal tract. This perhaps has as much to do with the controversy over the special serotypes of *E. coli* as purely scientific considerations. I make this as the final point because I can recall my own hesitancy in regarding the 111, B_4 and 55, B_5 organisms as significant.

* * * *

In Michigan for a period of nearly 7 years we have been conducting investigations on hospital nursery outbreaks of infant diarrhea. Within the last 4 years our interest has been centered on the occurrence of the special coliforms. Our experience bears out the fact that serotypes 111, B_4 and 55, B_5 are closely associated with at least one kind of infant diarrhea. The evidence to date is rather convincing that the 111, B_4 type, at least, should be considered among the causative agents of diarrhea of the newborn.

During this period of concentration on *E. coli* types we have carried out laboratory and some field work on 13 outbreaks of diarrhea in nurseries. Statistics are not available for all of the outbreaks, but in the two largest ones *E. coli* 111, B_4 was isolated from a large percentage of diarrheal babies. In the remaining 11 investigations, the 111, B_4 type was found associated with diarrhea in 9 nurseries while the 55, B_5 type was present in a high percentage of diarrheal infants in a 10th nursery. In the 11th outbreak no known pathogens such as Salmonellae or Shigellae were found and neither of the two types of *E. coli*. Thus, in 12 out of 13 outbreaks either the 111, B_4 or the 55, B_5 type was associated with the diarrhea.

We have isolated the 111, B_4 type from over 225 different infants and the other type from 10.

It is worthy of mention that the one outbreak, in which neither of the special coliforms was present, was different in that both adults and infants were involved. Although our specimens came only from infants and children who were hospitalized, diarrhea was present in both adults and younger individuals throughout the city in which the hospital was located. No evidence of a viral agent was secured from an examination of blood and stools from the diarrheal infants.

We have, like everyone else, been curious about the occurrence of the special coliform types in normal newborn babies. Our work to date along this line has been limited but interesting. It suggests to us that more work is justified. From one of the Lansing hospitals which has been free of nursery diarrhea for nearly 6 years, our laboratories cultured the stools of 1200 newborn babies. In addition

we examined 900 meconium specimens from some of the same infants. Isolation of *E. coli* 111, B_4 was successful from 3 of the stools. The 3 infants excreting the organism did not have diarrhea at the time specimens were taken; one developed diarrhea within 3 to 4 days, the other two remained well. We obtained no *E. coli* special types from meconium examinations.

Naturally, in all of the outbreaks investigated it has been customary to take specimens from doctors, nurses, mothers, and other persons in contact with the babies. Our results have been disappointing. We obtained the 111, B_4 type from the stools of 4 nurses who were in direct contact with diarrheal infants, and from 2 mothers who had sick babies. I know, however, of an outbreak in which 9 of the nursery personnel were found to be carrying 111, B_4 organisms. Some of these individuals had had diarrhea just preceding culture.

One of the first and largest outbreaks involving *E. coli*, which was investigated by our Department, occurred in Port Huron. Dr. Cummings, our Director, did the field work on that occasion. He noted at the time that certain clinical manifestations were somewhat different than those he had seen in previous epidemics. He has characterized the disease at Port Huron as one of exacerbations and remissions. The common clinical picture in the infants was: elevated temperature, sometimes up to 104°F; leukocytosis; foul-smelling stools; diarrhea not necessarily profound; the infants were toxic, acidotic; dehydration was pronounced; vomiting occurred with large numbers of infants. According to Dr. Cummings' experience at the time, the high temperatures, the leukocytosis, the foul-smelling stools and the considerable number of remissions were unusual.

I am not, as you can well appreciate, prepared to discuss the clinical picture of outbreaks investigated by our department, or the treatment. Certain details, however, come to the attention of a bacteriologist which may be of interest. It is noteworthy that from some of the early outbreaks we isolated streptomycin-sensitive and chloromycetin-sensitive strains of 111, B_4[15]. Treatment with chloromycetin appeared to be successful. Later the organisms isolated were streptomycin-resistant and some resistance to chloromycetin was noted. In one hospital outbreak the chloromycetin resistance of 111, B_4 strains was marked and therapy was changed to terramycin or aureomycin. This was not uniformly successful. The antibiotic spectrum indicated that neomycin might be effective. Treatment with this drug has been successful.

Dr. Warren Wheeler of Children's Hospital, Columbus, Ohio, has had experience with an outbreak of diarrhea recently in which *E. coli* 111, B_4 was isolated. He has permitted me to say that treatment with neomycin was very satisfactory. Current practice makes use of neomycin in infant diarrhea in a dosage of 50 to 100 milligrams per kilogram daily, over a period of 7 to 10 days. In the Michigan hospital mentioned a moment ago, the dosage was adjusted on a 50 milligram per kilo basis.

Because of the variety of antibiotics used today, it is only sensible to determine the drug sensitivity of a strain of 111, B_4 or 55, B_5 at the beginning and during

the course of an outbreak. We now make this service routine and it appears to be appreciated by physicians.

I have been asked repeatedly, could these special coliform organisms, like Salmonella, be of animal as well as human origin? Apparently they can. Hans Fey[28] of Zürich, Switzerland, has just announced the finding of the 111, B_4 organism on the prepuce of a bull. The 55, B_5 type has been recovered by him from bovine mastitis.

Another finding that points to the resemblance of the special coliforms to Salmonella is the fact that 111, B_4 and *Salmonella adelaide* are completely similar insofar as their 0 antigens are concerned. Since 0 antigens apparently account for virulence, you have an answer as to why this coliform is different from most members of its genus.

In conclusion, weary though you may be of hearing the formulae 111, B_4 and 55, B_5, I urge that you keep them in mind—particularly when you have cases of infant diarrhea under your care.

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LATE COMPLICATIONS IN JUVENILE DIABETES

THADDEUS H. JOOS, M.D.*

Since the introduction of Insulin in 1922, some 120 children with diabetes mellitus have been treated in the Pediatric Department at the Henry Ford Hospital. This paper deals with our experience in thirty-one of these patients followed ten or more years.

In general, our results are in agreement with those published by Walker (1), Post and Stickle (2), and Root, Sinden and Zanca (3). That is, the better the control, the fewer the complication, the most common of these being retinal hemorrhages and albuminuria, which were found in a sizable number of these patients.

COMPLICATIONS FOUND IN JUVENILE DIABETES IN FOUR SERIES

Table No. 1

	HFH	Walker	Post & Stickle	Root
Retinopathy	30 percent	46.6 percent	54 percent	56 percent
Cataracts	3 percent	14.6 percent		
Hypertension	3 percent	4.0 percent		36 percent
Albuminuria	30 percent	4.0 percent		26 percent
K.S.W.D.	7 percent			
Nephritis	9 percent			
Neuropathy	2 percent			

Of the thirty-one patients followed ten or more years, twenty exhibited at least one or a combination of several of the following changes: (1) Retinitis, (2) Albuminuria, (3) Cataracts, (4) Neuropathy, (5) Hypertension, and (6) Kimmelstiel-Wilson disease. Table two outlines the frequency.

TYPES OF COMPLICATIONS AND NUMBER OF LESIONS IN PATIENTS FOLLOWED TEN OR MORE YEARS

Table No. 2

Retinitis	Albuminuria	Cataracts	Neuropathy	Hypertension	KSWD	Nephrosis
10	10	1	1	1	2	3

The degree of each varied as to severity and physical disability, but one person died of Kimmelstiel-Wilson disease and another with bilateral cataracts had such extensive retinal hemorrhages that cataract removal was thought unwise.

When classifying control we used the number of times in coma and the positive Benedicts reaction of urines tested at home, as criteria. Table three illustrates this.

*Formerly Resident in Pediatrics.
At present with the U. S. Navy Medical Corps.

CLASSIFICATION OF CONTROL OF DIABETES

Table No. 3

	Coma	Positive Benedicts Test on Urine
Good	0	2 daily or less
Fair	1	2 daily or less
Fair to Poor	2 or 3	2 or 3 daily
Poor	4 or more	4 or more daily

In Table four the relationship between control and complications in the group can be seen.

CONTROL AND COMPLICATIONS

Table No. 4

Control	Patients with Complications No. Patients	Patients without Complications No. Patients
Poor	8	2
Fair to Poor	7	1
Fair	3	3
Good	2	5

There were six deaths recorded in the patients, five of whom died in our hospital and one in another institution. Coma claimed the lives of four, while pulmonary tuberculosis and Kimmelstiel-Wilson disease accounted for the other two.

DISCUSSION

The controversy between "free" and "controlled" diets we believe is swinging in favor of the controlled type of regime because of the increasing number of reports that control and complications are directly related[4,5]. Lichtenstein[6], when writing on the "free diet" in childhood diabetes gives his results on the basis of 10 years experience. He states that the number of complications encountered were few. We must, however, remember that seldom do any of the vascular changes make themselves evident until the child has had the disease at least ten years[7]. Our average time for the development of any of these changes was eleven years and eight months after the initial diagnosis of diabetes was established.

We believe our management where a moderate amount of carbohydrate is given and two positive Benedicts tests daily are allowed to guard against insulin reactions, affords a good middle ground to follow. As pointed out by John[8], when a person runs a positive Benedicts once a day we can assume that he is hyperglycemic about six hours out of 24. He goes on to say that a normal person with his post prandial hyperglycemia has high blood sugar levels approximately 25% of the time also.

With a diet in which the total calories are based on basal calories times 1.9 and with total calories from Protein 15%, Fat 50%, and Carbohydrates 35%, the child has a well balanced diet which is easily followed. Despite its relatively high fat content this diet had no ill effect on the blood cholesterol as determined in a limited number of our patients having the disease ten or more years. This diet provides the needed protein for sound continued growth, and on such a program all but a small number of our patients grew normally and remained well within the normals as given by Wetzel.[8]

CONCLUSIONS:

In the regulation of diabetes mellitus in children, control is of the utmost importance, since there is a steady accumulation of information showing that good control will lead to a lowered incidence of complications, especially retinopathy, hypertension, and albuminuria.

To obtain this control, a diet allowing a moderate amount of carbohydrate can be used with success. Such a diet has been used in the reported patients and may easily be prescribed as 15 percent of total calories from protein, 50 percent from fat and 35 percent from carbohydrate.

Doctor Nicholas G. Douvas kindly did the eye examinations and was of major assistance in this classification.

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RECENT THERAPY OF NEPHROSIS

A report of fifty-eight cases.

BERNARD A. O'HORA, M.D.*

The nephrotic syndrone in children has gained new interest with the introduction of antibiotics for the control of intercurrent infection, and, more recently through the use of ACTH in inducing diuresis and remission of symptoms of this disease. The nephrotic syndrone has long been characterized, and in the minds of most, differentiated from glomerulonephritis—by insidious onset, quite unlike that of glomerulonephritis, by the lack of impairment of renal function, by ability to resolve with complete recovery and by the unique susceptibility of its victims to pneumococcal bacteremia and peritonitis. It is this last feature which was responsible for the fatal outcome of most cases prior to 1937. In an effort to assess the present prognosis in lipoid nephrosis, our experience is here reviewed.

The well known disease of nephrosis is characterised by edema, albuminuria, low total blood proteins, especially the albumin, normal non-protein nitrogen, normal blood pressure, and absence of gross hematuria. The elevated blood lipids, especially cholesterol and lipoid bodies in the urine have lead to the associated term lipoid nephrosis.

The material studied consists of fifty-eight consecutive children diagnosed as lipoid nephrosis, or the nephrotic syndrone, admitted to the in-patient department over a period of twenty-five years from 1928 through 1953. All of these were, at the time of first admission, clinically and chemically "pure nephrotics" without evidence by history or laboratory determination of glomerulonephritis.

The group consists of twenty-three females and thirty-five males, ranging in age, at the onset of symptoms, from eleven months to nine years. The mean age of onset differed but slightly for the two sexes being thirty-seven months in the females and thirty-eight months in the males. More than eighty-five per cent of the group were between one and five years of age at the onset of symptoms.

It has been possible to follow forty-one patients, all but seventeen of the children, through the course of the disease to eventual recovery or death. Of the seventeen, ten are active cases still having symptoms of the disease and seven have failed to report for follow-up examinations.

The over-all results to date (8-1-53), may be summarized as follows: in Table 1 and Table 2.

Table 1—PRESENT STATUS OF FIFTY-EIGHT NEPHROTIC CHILDREN

	Number	Percent
Recovery	18	37.9
Mild Albuminuria only	4	
Died—Infection	7	32.7
Died—Uremia	12	
Lost to Study	7	12.1
Active, under Therapy	10	17.3
Totals	58	100.

*Resident—Department of Pediatrics.

Table 2—PRESENT STATUS OF THE FORTY-ONE CLOSED CASES

	Number	Percent
Recovered	18	53.7
Mild Albuminuria	4	
Died—Infection	7	46.3
Uremia	12	

From this it will be seen that slightly more than half of the cases, followed to conclusion, may be classified as recoveries. The advent of chemotherapy and antibiotics has altered the prognosis somewhat since all three of our deaths prior to 1937 were due to pneumococcal peritonitis. Since that time only four have died of infection, two of peritonitis, one of lobar pneumonia following varicella, and one of recurrent pleurisy with effusions. The more recent deaths have been largely due to renal failure and have occurred primarily in those cases showing a "mixed" type of picture with a superimposed element of glomerulonephritis. As will be described, such involment has carried a very poor prognosis in our series.

Hematuria is not part of the usual picture seen in the "pure nephrotic" and when it occurs is usually interpreted as evidence of so called "mixed nephrosis" or "nephritic nephrosis" with the implication of a bad prognosis. Microscopic hematuria was a frequent finding in this group, appearing in twenty-five cases one or more times during the course of the illness. As an indication of prognostic significance it may be questioned, however, since six of these cases are known to have completely recovered, five are still active, with four of these apparently improving, and only eleven are known to have succumbed to the disease. By temporarily eliminating from consideration the remaining three cases in which no follow-up is available, it would seem that microscopic hematuria does not, in itself, carry a bad prognosis in the nephrotic child and must be assessed as a quantitative sign.

It is worthy of note that the same statement cannot be made when hematuria accompanies hypertension or azotemia, and this was the case in all eleven who succumbed, while those who survived demonstrated hematuria as an isolated complication.

Hypertension, as a complication is strongly indicative of a superimposed glomerulonephritis and carries a poor prognosis. Seven children in this series have shown definitely elevated blood pressures, a systolic of over 134 mm. Hg. and a diastolic of over 89 mm. Hg. Of this group only one has definitely recovered, one survives as an active case in poor condition and five are dead, uremia being the cause of death in all.

Azotemia is of even more serious prognostic importance. Fifteen children in this series have exhibited blood non-protein nitrogens of 50 mgm. per cent or over, and of these thirteen are dead, one is active and in poor condition, the same case mentioned above as having hypertension, and the other has been lost to study.

Duration of symptoms from onset to eventual recovery or death has ranged from three months, (two cases, one recovery and one death) to over eight years

(one recovery). The usual course has been eighteen to thirty months in those recovering and twenty-four to thirty-six months in those terminating fatally.

Therapy has varied widely over the twenty-five year period covered in this series and it is difficult to credit any single measure, excepting the antibiotics, with contributing to an improved prognosis. General measures used in the group have included transfusions, plasma, concentrated plasma, salt-free albumin, cevitamic acid, thyroid extract, forced high protein diets to the point of leaving in place a polyethylene tube, and low salt diets. The antibiotics have assuredly reduced the mortality due to intercurrent infection, so prevalent in this disease. It might also seem that they would also be of benefit in preventing superimposition of glomerulonephritis, but in our experience this has not been the case. At least four of our uremic deaths have occurred in patients who developed "mixed nephrosis" while on prophylactic antibiotics or chemotheraputic agents. The mechanism here is obscure but it would appear that it is not identical to the pattern usually seen in the development of acute glomerulonephritis following streptococcal infection.

The introduction of adrenal corticotrophic hormone (ACTH) has opened a new phase in the management of nephrotic children. In our series fifteen children have been given a total of twenty-six courses of ACTH. The over-all results of these have been diuresis with remission of symptoms in seventeen instances involving ten children. In one instance the remission was permanent with no recurrence of symptoms and negative urine findings twenty-six months after treatment. A second case has had no edema for thirty-nine months following a course of ACTH but still has a mild albuminuria. Remissions in the other cases have been only temporary. One child has had diuresis following each of four courses of ACTH over a fifteen-month period. Most of our cases not responding to ACTH were among the early cases treated with this drug and were given inadequate dosages in the light of more recent experiences. Our current program is based on the use of forty units of ACTH per day in four doses for a period of ten days. The presence of hypertension or azotemia contraindicates the use of ACTH in our hands. There have been no untoward effects noted to this program.

SUMMARY

1. Fifty-eight cases of Nephrosis seen in the Department of Pediatrics over the past twenty-five years are reviewed.

2. Slightly better than one-half of those patients, twenty-two of forty-one followed for the entire course of the disease, experienced clinical recovery.

3. The development of transient microscopic hematuria by nephrotic children, in the absence of other complications, does not alter prognosis.

4. Development of azotema and/or hypertension is of serious prognostic import.

5. Antibiotic and chemotheraputic agents, have greatly reduced mortality due to intercurrent infections to which nephrotic children are peculiarly prone.

6. ACTH has proven of substantial value in inducing temporary, and in some few cases apparently permanent, remission of symptoms in the nephrotic syndrone.

THE AUDIOLOGY AND SPEECH CLINIC

A. Bruce Graham, Ph.D.*

An Audiology and Speech Clinic was first organized within the Division of Otolaryngology at Henry Ford Hospital in September, 1952, and was designed to be closely interrelated with many other divisions of the hospital. Similar clinics are found in university centers and in a limited number of medical centers throughout the United States.

The purpose of such a clinic is to provide a center for the diagnosis and rehabilitation of all types of hearing and speech problems in both children and adults and to promote research in these fields.

Within the area of hearing the audiological evaluation, which may include pure tone audiometry by both air and bone conduction and speech audiometry to determine both speech reception thresholds and the discrimination ability of the patient, provides the otolaryngologist with information which is valuable in the diagnosis of the type of hearing loss which exists as well as assisting in the determination of whether or not medical or surgical rehabilitation of the loss is possible. Specifically, carefully calibrated equipment and controlled testing routines can establish the presence of either a conductive or perceptive type reduction in auditory acuity or a combination of the two. Research in the area has also shown that there are many audiometric configurations which are indicative of specific pathologies within the ear. Combined otolaryngological and audiological findings are thus critical to a full evaluation of hearing problems. If the loss is not remissible through the use of medication or surgery, but is found to be either static or progressive, appropriate recommendations for audiological rehabilitation are made. Depending upon the individual case these may include the use of amplification to provide speech at a practical or usable level, lipreading training to supplement the auditory cues, auditory training either in the use of a hearing aid or more adequate employment of the auditory stimuli available to the individual with his particular type of loss. One common misconception regarding hearing losses is that a hearing aid will compensate for any type of loss. However, in many instances amplification provides no practical help. At best the individual finds that the use of a hearing aid produces problems for which the audiologist can provide aid. It is the responsibility of the hearing and speech clinic to determine, through appropriate tests, the advisability of a hearing aid and to help the individual in his adjustment to the use of amplification. In many instances a speech conservation program is needed to prevent the deterioration of speech in an individual who no longer hears his own voice normally. All of these services are available to the hard of hearing adult at the Audiology and Speech Clinic.

With the hard of hearing or deaf child the problem is generally more complex. Critical to the rehabilitation program is the age of onset and the degree of the loss.

*Audiologist, Division of Otolaryngology.

The child who is born deaf and cannot learn speech in the usual way will need a total special educational program which will include training in lipreading, auditory training, and speech and language development. The child who becomes hard of hearing after the onset of speech may only need special training in lipreading, auditory training, and speech within the regular school program. Just as children without hearing cannot learn to speak so children with peculiarities of hearing patterns will learn to speak as they hear. For example, one of the most misunderstood types of hearing loss is that in which the child has normal hearing for the low tones and a high frequency loss. Because the child hears the basic tones of the human voice and many sounds in his environment he responds adequately enough to most stimuli and is not thought to have a hearing loss. However, this child would not be expected to refine his infantile type of speech and would be considered by many to speak "baby talk." This is the child that many parents and teachers feel is not paying attention because they have no explanation for the fact that the child responds to many sounds, but still does not seem to understand everything asked of him. Part of the role of any hearing and speech clinic is to bring about a greater understanding of such problems through parent and teacher guidance. The prognosis for the adjustment of a deaf or hard of hearing child to a hearing world is closely related to adequate diagnosis. The earlier a diagnosis of deafness can be made in a child and appropriate rehabilitation measures begun, the greater are the chances for complete adjustment to a hearing world. Because local public school facilities for the rehabilitation of the young deaf and hard of hearing are readily available, the Clinic serves predominantly as a diagnostic center with these children. However, with the very young child, the Henry Ford Hospital Clinic can provide, through parent guidance and also direct training, the background for communication skills which will assist the child in a better adjustment to the special educational handling when he reaches the age at which the schools will accept him.

Within the area of speech defects one of the common problems is that of the child with delayed speech. This is the child in whom the onset of speech has not occurred within the usual range of readiness. In a majority of cases these problems are referred through pediatricians since the family generally seeks the advice of the child's doctor regarding why he has not begun to talk. Quite frequently it is assumed that this child must not hear adequately. The determination of the etiology of delayed speech, however, is most complex. Many factors may contribute to this retardation of speech, but the speech pathologist is concerned with four major areas in his differential diagnosis. Basically, he must determine whether or not a hearing loss of sufficient degree exists. Secondly, marked mental retardation will cause a delay in the development of speech. Such mental inadequacy may appear in the child as an apparent hearing loss because he lacks sufficient alertness to respond to auditory stimuli in the normal way. A third item of importance is the possible existence of psychological problems so severe that the child maintains no contact outside of himself and therefore does not respond to either speech or the gross sounds in his environment. A fourth, and very important factor which contributes to delayed speech is aphasia. Obviously, the therapeutic approach to a delayed speech problem will be altered considerably by adequte knowledge as to etiology. Certainly the child needing psychiatric

care for himself and parents should not be assigned to a school for the deaf. Problems of this nature demand the coordinated efforts of many divisions within the hospital in order to provide adequate diagnosis.

A second major speech problem is that of articulatory disorders. These children are the ones spoken of as not talking clearly or plainly. Basically, articulation problems may be either organic or functional and may possess a wide range of causal factors in either area. Again a team of medical and educational specialists may be needed for both diagnosis and therapy. The child with a cleft palate is a classic example of the necessity of cooperative functioning of many divisions within a medical center. The oral surgeon is concerned with functional closure of the cleft. In many cases where such closure is impossible because of an inadequacy of tissue the prosthodontist may provide artificial closure including speech appliances. Because of the many problems associated with cleft palate the orthodontist, pediatrician, and otolaryngologist, to name a few, may also contribute to the rehabilitation. The total evaluation of the individual's needs provides the framework for the type of speech training planned for the child. In many fortunate instances no speech therapy is necessary, but in others it is a prolonged affair covering years of concentrated effort.

The cerebral palsied child also demands the services of a group of specialists. In cases uncomplicated by mental deficiency, hearing losses, and aphasia, the coordinated efforts of the speech therapist, occupational therapist, and physical therapist can be expected to bring about a greater adjustment through providing a means of communication, an increased capacity for independence through self-help in dressing, feeding, and other activities. The careful evaluation of the type of cerebral palsy and the individual's potentiality to improve is critical to planning the therapeutic program.

In recent years a new speech problem has been added to the group with which the speech pathologist is concerned. Modern medicine has vastly increased the number of bulbar polio cases which survive. In many of these cases both a voice and articulation problem exists which resembles that of cleft palate speech. Instead of any inadequacy of tissue here, however, there is an inadequacy or weakness of function particularly of velo-pharyngeal closure. Since all but three sounds in the English language require varying degrees of velo-pharyngeal valving, there is a considerable degree of involvement of the articulation for speech as well as a change in voice quality, as a result of the excessive nasal emission of air.

As a result of brain damage due to war injuries a considerable amount of research has been carried out in the area of aphasia. This research has provided more appropriate methods of rehabilitation for individuals suffering a loss of speech following cerebral vascular accidents. In general, one thinks of adults only, particularly older adults, in conjunction with aphasia. However, the same condition may exist in brain damaged children as well. In children, the problem is more complex because there is no former capacity against which to compare nor on which to base the training program. Nevertheless, although the prognosis is slow, the adequately trained speech therapist can expect to contribute considerably toward the rehabilitation of many aphasic patients. The extent of

the lesion, age, pre-trauma intellectual capacity, and other factors necessarily alter the expected result.

The laryngectomized patient, if cooperative, can expect to learn to use esophageal speech for more adequate communication. This type of speech, using "belching" as the basic tone to be articulated, can be refined to such a degree that there is again intonation to the voice.

The problem of stuttering is always a major one in any hearing and speech clinic. At Henry Ford Hospital the psychiatrist, psychologist, and speech pathologist cooperate in the diagnosis and planning of the rehabilitation program which will best suit the individual's needs.

In summary, the Audiology and Speech Clinic at Henry Ford Hospital functions in close cooperation with many other divisions in the diagnosis and rehabilitation of the speech and hearing handicapped of all ages and types.

International Symposium

THE DYNAMICS OF VIRUS INFECTION

October 21, 22, 23, 1953

The professional staff of The Henry Ford Hospital with the initial advice and support of The Board of Trustees and Dr. Robin C. Buerki, Executive Director, of the Henry Ford Hospital, is sponsoring an international symposium on the subject The Dynamics of Virus Infection. This symposium will be held at the Henry Ford Hospital, October 21, 22, and 23, 1953, in the new auditorium. The final program follows and has been prepared with the help of the advisory members, and looks to the future of virus disease.

Advisory Members:

Thomas Francis, Jr.	Professor of Epidemiology and Chairman Department School of Public Health, University of Michigan
Joseph E. Smadel	Physician in Chief, Department of Virus and Rickettsial Diseases, Army Medical Service Graduate School, Washington, D. C.
John G. Kidd	Professor of Pathology, Cornell University, College of Medicine, New York
Frederick D. Stimpert	Director, Microbiological Research, Parke, Davis and Company, Detroit

Local Members:

Frank W. Hartman, Chairman

Gerald A. LoGrippo, Vice-Chairman

Philip J. Howard

D. Emerick Szilagyi

Edward L. Quinn, Secretary

Program

1st Morning Session

Moderator: THOMAS M. RIVERS,
The Hospital of the Rockefeller Institute for Medical Research,
New York, N. Y.

Mechanisms of Virus and Rickettsial Infections

Welcome

9:00 a.m.	1. The Initiation of Cellular Infection by Viruses	Alfred Gottschalk, The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Melbourne, Australia
9:40 a.m.	2. Mechanisms of Penetration by Viruses	Alfred D. Hershey, Carnegie Institution of Washington, Cold Spring Harbor, Long Island, N. Y.
10:00 a.m.	3. Physical Factors in Virus Penetration	Theodore T. Puck, University of Colorado, Denver, Colorado
10:20 a.m.	General Discussion	

10:40-10:50 a.m.—Intermission

10:50 a.m.	4. The Development and Maturation of Viruses	Salvador E. Luria, University of Illinois, Urbana, Illinois
11:20 a.m.	5. Incomplete Forms of Viruses	Preben von Magnus, State Serum Institute, Copenhagen, Denmark
11:50 a.m.	6. Combination Forms of Virus Induced by Double Infection	George K. Hirst, The Public Health Research Institute of the City of New York, N. Y.
12:20 p.m.	General Discussion	
12:40 p.m.	Luncheon	

1st Afternoon Session

Moderator: JOHN G. KIDD,
Cornell University Medical College, New York, N. Y.

Mechanisms of Virus and Rickettsial Infections

2:00 p.m.	1. Cellular Metabolism and Virus Growth	F. C. Bawden, Rothamsted Experimental Station, Harpenden, Herts, England
2:30 p.m.	2. Plant Viruses and Proteins	Barry Commoner, Washington University, St. Louis, Missouri
2:50 p.m.	3. Abortive Infection with Viruses	Mark H. Adams, New York University College of Medicine, New York, N. Y.

3:10-3:20 p.m.—Intermission

3:20 p.m.	4. Metabolic Transformations in Virus Infected Cells	Seymour S. Cohen, University of Pennsylvania, Philadelphia, Pennsylvania
3:45 p.m.	5. Intracellular Sites Important to the Development of Animal Viruses	W. Wilbur Ackerman, University of Michigan School of Public Health, Ann Arbor, Michigan
4:10 p.m.	6. Enzymic Changes in Virus Synthesis	Earl A. Evans, Jr., The University of Chicago, Chicago, Illinois
4:40 p.m.	General Discussion	

2nd Morning Session

Moderator: ALBERT E. SABIN,
The Children's Hospital Research Foundation,
Department of Pediatrics, University of Cincinnati,
Cincinnati, Ohio

Ecology and Pathogenesis

9:00 a.m.	1. Ecology and Virus Reservoirs	Richard E. Shope, The Rockefeller Institute for Medical Research, New York, N. Y.
9:40 a.m.	2. Ecologic Aspects of Transmission and Pathogenesis with Special Reference to Rickettsiae	J. Ralph Audy, Scrub Typhus Research Unit, Institute for Medical Research, Kuala Lumpur, Malaya
10:10 a.m.	3. Maintenance of Yellows Type Viruses in Plant and Insect Reservoirs	Louis O. Kunkel, The Rockefeller Institute for Medical Research, New York, N. Y.
10:40 a.m.	4. The Influence of Host and Environment on Rickettsia	Winston H. Price, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland
11:10-11:20 a.m.—Intermission		
11:20 a.m.	5. Pathogenic Mechanisms of Virus Diseases	William McD. Hammon, University of Pittsburgh School of Public Health, Pittsburgh, Pa.
11:50 a.m.	6. Pathogenesis of Variola	A. W. Downie, University of Liverpool School of Hygiene, Liverpool, England
12:20 p.m.	General Discussion	
12:40 p.m.	Luncheon	

2nd Afternoon Session

Moderator: JOHN PAUL,
Yale University School of Medicine, New Haven, Connecticut

Mechanisms of Immunity

2:00 p.m.	1. Mechanism of Convalescent Immunity and How it may be Simulated	Jonas E. Salk, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania
2:40 p.m.	2. Sites of Immune Barriers in Poliomyelitis	David Bodian, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland
3:10-3:20 p.m.—Intermission		
3:20 p.m.	3. Mechanism of Active Induced Immunity with Attenuated Living Vaccines	Karl Habel, National Microbiological Institute, National Institutes of Health, Bethesda, Maryland
3:50 p.m.	4. Practical Application of Living Virus Vaccines	Hilary Koprowski, Viral Research, Lederle Laboratories, New York, N. Y.
4:20 p.m.	General Discussion	
6:30 p.m.	Dinner	

3rd Morning Session

Moderator: A. J. RHODES,
The Hospital for Sick Children
Toronto, Canada

Methods of Virus and Rickettsial Diagnosis

9:00 a.m.	1. Early Diagnosis of Psittacosis Lymphogranuloma Group	Karl F. Meyer, George Williams Hooper Foundation, University of California Medical Center, San Francisco, California
9:40 a.m.	2. Early Diagnosis of Pox Disease	F. O. MacCallum, Central Public Health Laboratory, London, England
10:10 a.m.	3. Early Diagnosis by Tissue Culture	Thomas H. Weller, The Children's Medical Center, Boston, Massachusetts
10:40 a.m.	4. Summary of Evaluation of Virus and Rickettsial Diagnosis	Edwin H. Lennette, Viral and Rickettsial Disease Laboratory, State of California Department of Public Health, Berkeley, California
11:10 a.m.-11:20 a.m.—Intermission		
11:20 a.m.	5. Early Detection of Antigen as a Diagnostic Method	John C. Snyder, Harvard University School of Public Health, Boston, Massachusetts
12:10 p.m.	General Discussion	
12:30 p.m.	Luncheon	

3rd Afternoon Session

Moderator: GILBERT DALLDORF,
Division of Laboratories and Research,
New York State Department of Health, Albany, N. Y.

Chemical Approaches to Prophylaxis and Therapy of Virus and Rickettsial Diseases

2:00 p.m.	1. Interference and Physical-Chemical Blockade	Frank L. Horsfall, The Hospital of the Rockefeller Institute for Medical Research, New York, N. Y.
2:30 p.m.	2. Nucleoprotein and Transforming Substances	Rollin D. Hotchkiss, The Rockefeller Institute for Medical Research, New York, N. Y.
3:00 p.m.	3. Nutritional Inhibitors	Aron F. Rasmussen, Jr., University of California Medical Center, Los Angeles, California

3:30 p.m.-3:45 p.m.—Intermission

3:45 p.m.	4. Inhibitors of Virus and Rickettsial Multiplication	Dillworth W. Woolley, The Rockefeller Institute for Medical Research, New York, N. Y.
4:15 p.m.	5. Suppression of Growth by Clinical Antibiotics	I. William McLean, Jr., Microbiological Research, Parke, Davis & Company, Detroit, Michigan
4:45 p.m.	6. Clinical Application and Mode of Action	Theodore E. Woodward, University of Maryland School of Medicine, Baltimore, Maryland
5:15 p.m.	General Discussion	

THE HENRY FORD HOSPITAL MEDICAL SOCIETY
PROGRAMS FOR THE FALL OF 1953

October 22, 1953, Thursday, 8:45 P.M. — Grand Ballroom — Hotel Statler

(Meeting in conjunction with International Virus Symposium)

Problems of Diagnosis in Virus Diseases.
Frank L. Horsfall, M.D., Hospital of the Rockefeller Institute of Medical Research.

November 10, 1953, Tuesday, 8:15 P.M. — Henry Ford Hospital Auditorium

Tissue Culture Techniques in Investigative Dermatology.
Clarence S. Livingood, M.D., Chief of Division of Dermatology, Henry Ford Hospital, and Funan Hu, M.D., Research Associate in Division of Dermatology, Henry Ford Hospital.

December 8, 1953, Tuesday, 8:15 P.M. — Henry Ford Hospital Auditorium

Some results of the Application of Electron Microscopy to Medicine. The Edsel B. Ford Lecture. James Hillier, Ph.D., Research Physicist, R.C.A. Laboratories, Princeton, N. J.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

HYPERCHLOREMIC ACIDOSIS; A STUDY OF THE MECHANISM IN URETEROSIGMOIDOSTOMY.

A. Waite Bohne and C. E. Rupe, Surg., Gynec. & Obst. 96:541, 1953.

Uretero-sigmoidostomy is followed in a large proportion of cases by hyperchloremic acidosis. Two hypotheses have been held regarding its cause: first, reabsorption of urinary chloride by the sigmoid mucosa, and second renal damage incident to infection and obstruction producing functional derangement. The rates of chloride absorption from the sigmoid were studied, and found to be influenced by chloride concentration, by the presence of phosphate, and, apparently, by the hydrogen ion concentration of the sigmoid contents. Formulae and examples are shown of the quantitative amount of chloride reabsorption. The frequent clinical observation of reversal of the acidosis by rectal tube drainage is evidence against the role of the kidney in this acidosis.

INTRAMEDULLARY WIRE FIXATION OF HAND FRACTURES.

Robert H. Clifford. Plastic & Reconstruct. Surg. 11:366, 1953.

In 1949, the use of immediate intramedullary wiring in fractures of the metacarpals was described. Intramedullary wire fixation is a method of treatment well suited to fractures of the hand because the position of the fragments can almost always be palpated. There is no strong muscle pull, and the fractures can usually be reduced easily. The method has been used in 36 cases in the past two years, with only one slight infection. The method is easily effected, affords excellent fixation, and maintains full mobility of the rest of the hand.

RADIOLOGICAL STUDY OF THE TEMPOROMANDIBULAR JOINTS.

Howard P. Doub and Fred A. Henny. Radiology 60:666, 1953.

Study of the temporo-mandibular joints calls for special roentgen technic and a thorough understanding of the anatomy and physiology of these joints.

The complaint of crepitation, snapping and disorder of movement of the temporo-mandibular joints is fairly common, and more attention should be devoted to their roentgen study. Mandibular movements are of hinge, gliding and rotary types. Anatomic types are the normal joint, the flattened gliding joint, and the marked convex joint. A description is included of the gross anatomy, and clinical findings associated with disease and injury. The roentgenographic technic used is described, and has shown the morphologic changes associated with injury, arthritis, and other diseases.

CHOLECYSTO-DUODENO-COLIC LIGAMENT CAUSING HIGH GRADE OBSTRUCTION OF THE DUODENUM: Report of a case. L. J. GREGORY, R. J. PRIEST and J. BARRON. Gastroenterology 23:659, 1953.

High grade duodenal obstruction caused by a cholecysto-duodeno-colic ligament is rare. Neff and Haden reported two cases of complete duodenal obstruction of this type in children. Death occurred in both instances from alkalosis. Necropsy revealed a cholecysto-duodeno-colic ligament tightly compressing the duodenum at the junction of the first and second portions. Solem reported three cases with clinical signs of high obstruction. In none of his cases was obstruction complete.

This successfully operated case is of interest because of the extreme degree of duodenal obstruction produced by a cholecysto-duodeno-colic ligament. This occurred in a healthy, young man who had been under our observation during his adolesence.

AN UNUSUAL TYPE OF OXYGEN TENT MAKING USE OF LIQUID OXYGEN. FRANK W. HARTMAN and VIVIAN G. BEHRMANN. Hospitals 27:111, April 1953.

Liquid oxygen tents have replaced the conventional type electrically cooled tents in the Henry Ford Hospital since 1938. Trial and experiment with these have been carried on since 1934.

Two models of liquid oxygen tents, Model A and B, have been perfected from the early types. Model A operates on convection circulation which is adequate because the differential in temperature between the cooling chamber and the tent is so large, i.e., 70°-100° F. Model B makes use of a sparkless motor to circulate the air from the tent to the surface of the liquid oxygen in the six-gallon vacuum jar, thus eliminating wicks and making thermostatic control easy and accurate. Economy is effected by small manufacturing cost, low maintenance cost, low service cost, and, finally, low cost of liquid oxygen.

PRESENT STATUS OF PLASMA EXPANDERS. FRANK W. HARTMAN and VIVIAN G. BEHRMANN. J.A.M.A. 152:1116, 1953.

The term "plasma expanders" is now used by the National Research Council and seems the logical name for this group of substances. The desirable properties of a plasma expander should include a molecular size large enough for 50% to be retained for 24 hours; isotonicity, sedimentation rate, osmotic pressure, and viscosity comparable to that of plasma; a molecular structure allowing slow metabolism, but not subject to prolonged tissue storage; freedom from pyrogenic, allergic, antigenic, or toxic properties; and reproducibility, and stability. There are three classes of macromolecular substances found worthy of consideration as plasma extenders. These are proteins, including serum albumin, globulin, bovine plasma, and the gelatins; carbohydrates, including gum acacia, glycogen, pectin, dextran, and okra; and the synthetic polymer, polyvinylpyrrolidone. The data from experimental work done on samples of these classes of material, support the view

that the gelatins are the most promising class of substances. The emergency use of dextran and polyvinylpyrrolidone in limited quantities as well as gelatin is justified in shock states.

GIANT INTRAMURAL LEIOMYOMA OF ESOPHAGUS. Case Report. LEO J. KENNEY. J. Thoracic Surg. 26:93-100, July, 1953.

The case presented here is of interest because it concerns a tumor that is encountered very infrequently, and, in this particular instance the lesion had attained such a great size that its surgical management necessitated an operative procedure of unusual magnitude. This is believed to be the fourth such case recorded that survived a radical esophagectomy and esophago-gastrostomy. It is thought to be the largest esophageal tumor (1420 gm) ever resected surgically. The method of jejunal alimentation which was used in the management of the esophagopleural-cutaneous fistula that developed in this patient, was eminently successful in maintaining nutrition.

SPACE GROUP AND CELL CONSTANTS OF 3, 4, 5-TRICARBETHOXY PYRAZOLE. JONATHAN PARSONS. Acta Crystallographica 6:367, 1953.*

A space-group determination has been made for a crystalline derivative of pyrazole tricarboxylic acid, using the Weissenberg X-ray method. This compound, 3,4,5-tricarbethoxy pyrazole, was isolated in the Biochemistry Department of the Institute, using the method of Curtius (1915).

Rotation and Weissenberg photographs were prepared for the b and c axes of a single crystal of this compound. The only systematic absences found were for OkO when k is odd. This indicates that the space group is either $P2_1$—C_2^2 or $P2_1/m$—C_{2h}^2. Measurement of the unit-cell dimensions from the central lattice line spacings on the zero-layer photographs led to the following lattice constants:

$a = 9.60$, $b = 7.33$, $c = 10.38$ A, and $\beta = 97° 35' \pm 15'$.

The inclination angle β was measured using the method of angular lag (Buerger, 1942).

The approximate density of the crystals was found to be 1.3 g.cm. $^{-3}$ by flotation in mixtures of benzene and carbon tetrachloride. The density computed from X-ray data on the assumption of two molecules per unit cell is 1.304 g.cm.$^{-3}$. The presence of two rather than four molecules per unit cell is rather strong evidence for the space group $P2_1$ rather than $P2_1/m$ as, for the latter space group, the molecule would have to be centro-symmetrical.

A table gives the powder pattern d values and visual estimates of their relative intensities.

SIMPLE AGITATION DEVICE FOR HIGHLY RADIOACTIVE VOLUMETRIC FLASKS. L. E. PREUSS. J. Scient. Instruments 30:252, 1953.*

Quantitative work with radioactive solutions involve, for the most part, the use of ordinary volumetric flasks in all size ranges. The handling of these flasks

*From Edsel B. Ford Institute for Medical Research.

becomes a problem if primary dilutions are above 25mC in activity. These conditions are frequently met when opening shipments and in the preparation of therapeutic amounts of the solutions. Accurate calibration by dilution methods often necessitate that the flask contents be carefully agitated by inversion. These procedures require some remote control device which will grasp the various flasks and allow them to be inverted while coincidently holding the stopper in place.

Such a remote handling device has been developed here. A detailed sketch of its working parts and a photograph are shown.

RUGGED SCINTILLATION-COUNTER HOUSING FOR BIOLOGICAL APPLICATIONS. L. E. Preuss. Nucleonics 11:74, 1953.*

The scintillation counter is particularly useful in biological and clinical tracer research because of its high gamma sensitivity. Such applications frequently necessitate rough handling of the instrument, while the scintillation counter itself is best adapted to bench work. This rugged use in biological applications demands a special and sturdy design.

A housing is described which is portable, operates in any position, is sturdy enough to serve as a base for heavy lead and magnetic shielding, and allows good optical coupling, with an efficient reflecting surround. The surround, also, is kept at a very low concentration of available moisture. Finally, the device allows simple assembly under dry-box conditions with easy replacement of crystal and photomultiplier.

STRUCTURAL CHANGES IN SENSITIZED HUMAN ERYTHROCYTES OBSERVED WITH THE ELECTRON MICROSCOPE. John W. Rebuck. Anat. Rec. 115:591, 1953.

Electron microscopy of intact erythrocytes from a case of acquired hemolytic anemia revealed peripheral filamentation across the plasma-corpuscular shrinkage space not present in controls. These filaments were composed of delicate strands of plasma (presumably the autoagglutinins demonstrable serologically) adherent to minute, elevated segments of the surface ultrastructure. Measurements of the affected segments revealed that they were of the same width as the strands of fibrillar cytoskeleton of the defatted erythrocytic ghosts depicted by Wolpers.

Action of Anti-A antibody upon Group A erythrocytes produced a distinguishable structural change in that pulled-out segments of the surface ultrastructure presented flat, plateau-like summits in contrast to the more rounded or spiculated projections of classic crenation. Such affected segments were 6 to 24 times the breadth of the fibrils of the cytoskeleton or its interstices, a finding consistent with the concept of the abundance of antigens of the A-B-O system in or on the erythroctyte.

Anti-Rh antibodies produced similar but smaller and less frequent distortions of the surface ultrastructure.

The relation of the structural receptor sites to antigenic sites was discussed in the light of the reported literature concerning the chemistry of the blood group substances.

Electron micrographs of agglutinated ghosts of erythrocytes were presented as evidence that sites of agglutinogenic activity were, located in these experiments, in the surface ultrastructure. Sickle-cell ghosts which retained the bizarre outline of the intact meniscocyte were obtained similarly by exposure to their specific agglutinins during the period of hemolysis.